STRIDE-1 Phase 3 Trial of AXS-05 in TRD
Topline Results
Conference Call

March 30, 2020
## AXS-05 in Treatment Resistant Depression (TRD) STRIDE-1 Phase 3 Trial Topline Results

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Mark Jacobson, Chief Operating Officer</td>
</tr>
<tr>
<td>Overview and Summary</td>
<td>Herriot Tabuteau, MD, Chief Executive Officer</td>
</tr>
<tr>
<td>STRIDE-1 Trial Design &amp; Results</td>
<td>Cedric O’Gorman, MD, Senior Vice President, Clinical Development &amp; Medical Affairs</td>
</tr>
<tr>
<td>KOL Perspective of STRIDE-1 Data</td>
<td>Maurizio Fava, MD, Psychiatrist-in-Chief at Massachusetts General Hospital (MGH), Director of the Division of Clinical Research of the MGH Research Institute, Associate Dean for Clinical &amp; Translational Research at Harvard Medical School</td>
</tr>
<tr>
<td>Q&amp;A</td>
<td>Presenters, Nick Pizzie, Chief Financial Officer and Dave Marek, Chief Commercial Officer</td>
</tr>
<tr>
<td>Concluding Remarks</td>
<td>Herriot Tabuteau, MD, Chief Executive Officer</td>
</tr>
</tbody>
</table>
Certain information contained in this presentation may include “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials and the number or type of studies or nature of results necessary to support the filing of a new drug application for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration (“FDA”) or other regulatory authority approval of, or other action with respect to, our product candidates (including, but not limited to, FDA’s agreement with the Company’s plan to discontinue the bupropion treatment arm of the ADVANCE-1 study in accordance with the independent data monitoring committee’s recommendations); the Company’s ability to obtain additional capital necessary to fund its operations; the Company’s ability to generate revenues in the future; the potential for the MOMENTUM clinical trial to provide a basis for approval of AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment; the potential for the ASCEND clinical trial, combined with the GEMINI clinical trial results, to provide a basis for approval of AXS-05 for the treatment of major depressive disorder and accelerate its development timeline and commercial path to patients; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company’s research and development programs and collaborations; the enforceability of the Company’s license agreements; the acceptance by the market of the Company’s product candidates, if approved; the Company’s anticipated capital requirements, including the Company’s anticipated cash runway; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. These factors could cause actual results and developments to be materially different from those expressed in or implied by such statements. Forward-looking statements are not guarantees of future performance, and actual results may differ materially from those projected. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, these projections, assumptions and estimates are necessarily subject to a high degree of uncertainty and risk.
Summary and Overview

Herriot Tabuteau, MD
Chief Executive Officer
Axsome Therapeutics, Inc.
Summary of Topline Results:
Rapid and Significant Effects with AXS-05 in TRD Patients

- AXS-05: a novel, oral, investigational NMDA receptor antagonist with multimodal activity
- Rapid and statistically significant improvements in MADRS versus bupropion at Weeks 1, 2, and overall (key secondary endpoints)
- Numerical separation from bupropion at all timepoints, statistical significance not reached on primary endpoint (Week 6)
- Rapid and highly statistically significant induction of remission on the QIDS-SR-16 (score of ≤ 5) as compared to bupropion starting at Week 1, with significance maintained at every point thereafter
- AXS-05 demonstrated statistically significant improvements in cognitive function and reduction in anxiety symptoms versus bupropion
- AXS-05 was generally safe, well tolerated, and not associated with psychotomimetic effects, weight gain or sexual dysfunction
- These results support continued development in TRD with initiation of second Phase 3 trial anticipated 3Q 2020
- On track for planned NDA filing for Breakthrough Therapy designated AXS-05 in MDD for 4Q 2020
Depression is a disabling and potentially life-threatening, biologically-based disorder.

17 million U.S. adults experience major depressive episodes each year and at least one-third of them are considered treatment resistant.\(^1,2\)

Patients are considered treatment resistant if they have not responded adequately to at least 2 different anti-depressants of adequate dose and duration in the current depressive episode.\(^2\)

Treatment resistant depression is a chronic disorder associated with high economic burden, significantly impacted quality of life and various comorbid conditions.\(^3\)

Limited treatment options are available.

Urgent need exists for new treatments that have rapid and significant efficacy, are safe and well tolerated, and offer convenient administration.

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AXS-05: Novel, Oral, NMDA Receptor Antagonist with Multimodal Activity

NMDA Receptor Antagonism

Modulation of DM Delivery

AXS-05

dextromethorphan/bupropion modulated delivery tablet

Sigma-1 Receptor Agonism

Monoamine Reuptake Inhibition

Abbreviations: DM = Dextromethorphan; Mg²⁺ = magnesium ion; Na⁺ = sodium ion; Ca²⁺ = calcium ion; K⁺ = potassium ion. Axsome data on file
STRIDE-1 Phase 3 Trial
Design & Results

Cedric O’Gorman MD, MBA
Senior Vice President, Clinical Development and Medical Affairs
Axsome Therapeutics, Inc.
A Phase 3 trial to assess the efficacy and safety of AXS-05 in the treatment of TRD

1:1 randomization of inadequate responders

Period 1, Open-label (6 weeks)  Period 2, Double-blind (6 weeks)

Open-Label Bupropion
(150 mg BID)

AXS-05
(45 mg DM / 105 mg BUP BID)

N=156
N=156

Bupropion
(150 mg BID)

N=799

BID = twice daily; BUP = Bupropion; DM = Dextromethorphan.

**Primary Endpoint:** Change in depression score from randomization to end of study, measured using the Montgomery-Åsberg Depression Rating Scale (MADRS)

**Key Secondary Endpoints:**
- Change from baseline in MADRS at week 2 post-randomization
- Change from baseline in MADRS at week 1 post-randomization
- Overall treatment effect on MADRS total score
- Change from baseline in Sheehan Disability Scale (SDS) at week 6 post-randomization
Inclusion criteria included:

Open-label Period
– Male or female 18-65 years of age inclusive
– History of inadequate response to 1 or 2 prior antidepressant treatments, established by ATRQ
– Hamilton Depression Rating Scale (HAMD-17) total score of ≥ 18

Double-blind Period
– Inadequate response to 2 or 3 prior antidepressant treatments, including open-label period failure

Exclusion criteria included:
– History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current episode or in the past 6 months
– Schizophrenia, bipolar disorder, obsessive compulsive disorder
– Psychiatric symptoms secondary to any other general medical condition
STRIDE-1 Phase 3 Trial: 
Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AXS-05 (45 mg DM / 105 mg BUP)</th>
<th>Bupropion (150 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>44.3 (12.19)</td>
<td>45.1 (12.56)</td>
</tr>
<tr>
<td><strong>Female Gender, n (%)</strong></td>
<td>101 (65.6%)</td>
<td>97 (62.6%)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>100 (64.9%)</td>
<td>106 (68.4%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>41 (26.6%)</td>
<td>39 (25.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.3%)</td>
<td>6 (3.9%)</td>
</tr>
<tr>
<td>Other or Not Reported</td>
<td>11 (7.1%)</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td><strong>BMI (mg/kg²)</strong></td>
<td>29.9 (5.85)</td>
<td>29.5 (5.64)</td>
</tr>
<tr>
<td><strong>MADRS Total Score</strong></td>
<td>33.4 (5.61)</td>
<td>33.2 (5.17)</td>
</tr>
<tr>
<td><strong>CGI-S Score</strong></td>
<td>4.6 (0.61)</td>
<td>4.6 (0.54)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated.
Abbreviations: BMI = Body Mass Index; BUP = bupropion; CGI-S = Clinical Global Impression – Severity; DM = dextromethorphan; MADRS = Montgomery-Åsberg Depression Rating Scale

- Demographics and baseline characteristics were similar across both treatment groups
- Study completion rates were similar across both treatment groups, 89% for AXS-05 and 94% for bupropion
Improvement in Depressive Symptoms: Change in MADRS Total Score

**Primary Endpoint:** Change in MADRS Total Score at Week 6
- **AXS-05 (n=154):** -11.6
- **Bupropion (n=155):** -9.4
- **Difference:** -2.2
- **P-Value:** NS

**Key Secondary Endpoints:**
- Change in MADRS Total Score at Week 1
  - **AXS-05:** -5.2
  - **Bupropion:** -3.6
  - **Difference:** -1.6
  - **P-Value:** 0.020
- Change in MADRS Total Score at Week 2
  - **AXS-05:** -8.0
  - **Bupropion:** -6.1
  - **Difference:** -1.9
  - **P-Value:** 0.035
- **Overall treatment effect on MADRS Total Score**
  - **AXS-05:** -8.6
  - **Bupropion:** -6.7
  - **Difference:** -1.9
  - **P-Value:** 0.031

Notes: P-values calculated from LSMean. Abbreviations: BID = twice daily; MADRS = Montgomery-Åsberg Depression Rating Scale
Improvement in Depressive Symptoms: Change in the QIDS-SR-16

Notes: P-values calculated from LSMean.
Abbreviations: BID = twice daily; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report-16 Item
Improvement in Depressive Symptoms: Achievement of Remission (QIDS-SR ≤ 5)

Notes: P-values calculated from LSMean. Remission cut-off score of ≤5
Abbreviations: BID = twice daily; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report-16 Item
Improvement in Cognitive Function: Change in MGH-CPFQ-Cognitive Dimension

- Cognitive items of the CPFQ assess sharpness/mental acuity, and the ability to focus/maintain attention, to remember/recall information, and to find words.
- Each of the 4 items on the cognitive dimension of the CPFQ are scored 1-6, with lower scores representing improvements in cognitive functioning.

Notes: P-values calculated from LSMean.
Abbreviations: BID = twice daily; MGH-CPFQ = Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire.
## Safety Profile of AXS-05 in TRD: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Double-blind Period</th>
<th>Open-label Period</th>
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<tbody>
<tr>
<td></td>
<td>AXS-05 (N = 154)</td>
<td>Bupropion (N = 156)</td>
</tr>
<tr>
<td>Any TEAE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67 (43.5%)</td>
<td>61 (39.1%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 (8.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (5.2%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6 (3.9%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (2.6%)</td>
<td>7 (4.5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (1.9%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (1.9%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>2 (1.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: AE = adverse event. Data presented as number of subjects (% of subjects)

- Treatment-emergent AEs occurring in ≥3% of subjects during the open-label period or ≥5% of subjects during the double-blind period are reported.
- In double-blind period, treatment-emergent AE is defined as any AE with an onset on or after date of randomization and prior to or on visit 9 date or period 2 early termination date.

### Key Points:

- Rates of discontinuation due to adverse events were low in both groups; 2.6% for AXS-05 and 1.3% for bupropion.
- Three serious adverse events occurred in the AXS-05 arm: migraine, overdose, and suicidal ideation (8 days after subject completed treatment).
STRIDE-1 Phase 3 Trial Results: Summary

• AXS-05 met key secondary endpoints by rapidly improving symptoms of depression in patients with treatment resistant depression (TRD)

• AXS-05 demonstrated numerical improvement on primary endpoint (MADRS at Week 6) versus active comparator, but did not reach statistical significance

• Statistically significant greater rates of remission on the QIDS as compared to bupropion

• Statistically significant improvements with AXS-05 compared to bupropion in cognition and anxiety

• AXS-05 was generally safe and well tolerated in this trial, consistent with our prior experience with AXS-05
KOL Perspective on STRIDE-1 Data

Professor Maurizio Fava, MD

Psychiatrist-in-Chief at Massachusetts General Hospital (MGH)
Director of the Division of Clinical Research of the MGH Research Institute
Associate Dean for Clinical & Translational Research at Harvard Medical School
Q&A
Concluding Remarks

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.
# AXS-05: Clinical Programs in Psychiatry

<table>
<thead>
<tr>
<th>Indication</th>
<th>ASCEND</th>
<th>GEMINI</th>
<th>STRIDE-1</th>
<th>AXS-05 / OL</th>
<th>ADVANCE-1</th>
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</thead>
<tbody>
<tr>
<td>Phase</td>
<td>MDD</td>
<td>MDD</td>
<td>TRD</td>
<td>MDD/TRD</td>
<td>AD Agitation</td>
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<tr>
<td>Objectives</td>
<td>Efficacy of AXS-05 vs. BUP</td>
<td>Efficacy of AXS-05 vs. PBO</td>
<td>Efficacy of AXS-05 vs. BUP</td>
<td>Long-term safety of AXS-05</td>
<td>Efficacy of AXS-05 vs. BUP and PBO</td>
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<tr>
<td>Status</td>
<td>Completed</td>
<td>Completed</td>
<td>Completed</td>
<td>Ongoing</td>
<td>Dosing Complete</td>
</tr>
<tr>
<td>Subjects Dosed</td>
<td>96</td>
<td>326</td>
<td>310</td>
<td>876</td>
<td>&gt;360</td>
</tr>
</tbody>
</table>

Abbreviations: BUP = bupropion; MDD = Major Depressive Disorder; OL = Open-label; PBO = placebo; TRD = Treatment Resistant Depression

- NDA filing of AXS-05 in the treatment of MDD, based on positive results from GEMINI and ASCEND trials on track for 4Q 2020
- FDA Breakthrough Therapy designation granted in MDD, Fast Track designation in TRD and AD agitation
Our CNS Candidates and Pipeline

- Five differentiated clinical-stage CNS assets targeting significant and growing markets
- Patent protection to 2034-2036, worldwide rights for most product candidates

<table>
<thead>
<tr>
<th>Product Candidate</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXS-05 (DM + BUP)</td>
<td>Major Depressive Disorder: Breakthrough Therapy Designation</td>
<td>Treatment Resistant Depression: Fast Track Designation</td>
<td>Agitation in Alzheimer’s Disease: Fast Track Designation</td>
<td>CNS Disorders</td>
</tr>
<tr>
<td>AXS-07 (MoSEIC™ Mx + Riz)</td>
<td>Migraine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AXS-12 (Reboxetine)</td>
<td>Narcolepsy: U.S. Orphan Designation</td>
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<tr>
<td>AXS-14 (Esreboxetine)</td>
<td>Fibromyalgia</td>
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<tr>
<td>AXS-09 (DM + S-BUP)</td>
<td>CNS Disorders</td>
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Abbreviations: BUP = Bupropion; CNS = Central Nervous System; DM = Dextromethorphan; Mx = Meloxicam; Riz= Rizatriptan; S-BUP = Esbupropion.
# Our Clinical and Regulatory Milestones

<table>
<thead>
<tr>
<th>Product Candidate</th>
<th>Indication</th>
<th>2020</th>
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<tbody>
<tr>
<td>AXS-05 (DM + BUP)</td>
<td>MDD</td>
<td>● NDA submission (4Q)</td>
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<tr>
<td></td>
<td>TRD</td>
<td>● STRIDE-1 topline results</td>
</tr>
<tr>
<td></td>
<td>AD Agitation</td>
<td>✓ ADVANCE-1 Phase 2/3 topline results (early 2Q)</td>
</tr>
<tr>
<td></td>
<td>Smoking Cessation</td>
<td>● FDA meeting (2020)</td>
</tr>
<tr>
<td>AXS-07 (MoSEIC™ Mx + Riz)</td>
<td>Migraine</td>
<td>● INTERCEPT Phase 3 topline results (imminent) ● NDA submission (4Q)</td>
</tr>
<tr>
<td>AXS-12 (Reboxetine)</td>
<td>Narcolepsy</td>
<td>● Phase 3 trial start (2020)</td>
</tr>
<tr>
<td>AXS-14 (Esreboxetine)</td>
<td>Fibromyalgia</td>
<td>● FDA meeting (2020)</td>
</tr>
</tbody>
</table>

Abbreviations: AD = Alzheimer's Disease; BUP = Bupropion; DM = Dextromethorphan; MDD = Major Depressive Disorder; Mx = Meloxicam; Riz = Rizatriptan; TRD = Treatment Resistant Depression.  
✓ Accomplished milestone.  
● Upcoming milestone.
Thank you.

For more information, please contact
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